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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
BUNNER, BRIDGET E

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 10/03/2002 12

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application N .	Applicant(s)	
	09/905,088	ASHKENAZI ET AL.	
	Examin r	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendments of 12 July 2001 (Paper No. 5) and 27 August 2002 (Paper No. 11) have been entered in full. Claims 1-38 are cancelled and claims 39-51 are added.

Claims 39-51 are under consideration in the instant application.

Sequence Compliance

It is noted to Applicant that the STIC Systems Branch corrected a nucleic number at the end of a nucleic line, specifically SEQ ID NO: 173 in the CRF submitted 28 December 2001 (Paper No. 3).

Oath/Declaration

1. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

(a) Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

(b) It does not identify the citizenship of each inventor.

Specification

2. The disclosure is objected to because of the following informalities:

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (See pg 71, line 28; pg 154, line 17; pg 167, line 38; pg 178, line 34). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Appropriate correction is required.

Claim Objections

5. Claims 45-49 are objected to because of the following informalities: There is a "." missing after the recitation of the claim number.

Appropriate correction is required.

Claim Rejections - 35 USC § 101 and 35 USC § 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 39-51 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility. Novel biological molecules lack well established utility and must undergo extensive experimentation.

Specifically, claims 39-51 are directed to an isolated polypeptide having at least 80%, 85%, 90%, 95%, and 99% amino acid sequence identity to (a) the amino acid sequence of the polypeptide shown in Figure 86 (SEQ ID NO: 245), (b) the amino acid sequence of the polypeptide shown in Figure 86 (SEQ ID NO: 245) lacking its associated signal peptide, (c) the

amino acid sequence of the extracellular domain of the polypeptide shown in Figure 86 (SEQ ID NO: 245), (d) the amino acid sequence of the extracellular domain of the polypeptide shown in Figure 86 (SEQ ID NO: 245) lacking its associated signal peptide, or (e) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209393. The claims are also directed to an isolated polypeptide comprising the previously mentioned subparts (a), (b), (c), (d), or (e).

The specification asserts that the PRO293 polynucleotide (SEQ ID NO:244) and polypeptide (SEQ ID NO: 245) of the present invention have homology to leucine rich repeat proteins (pg 27-28, 48) The specification also discloses that portions of the PRO293 polypeptide have significant homology with the neuronal leucine rich repeat proteins 1 and 1 (NLRR-1 and NLRR-2) and possesses ligand-ligand binding activity typical of the NRLL protein family (pg 109, lines 23-31). However, the instant specification does not teach any significance or functional characteristics of the PRO293 polynucleotide (SEQ ID NO: 244) or polypeptide (SEQ ID NO: 245). The specification also does not disclose any methods or working examples that indicate the polynucleotides and polypeptide of the instant invention are involved in any activity, particularly ligand-ligand binding activity of the NRLL protein family. Since significant further research would be required of the skilled artisan to determine how the claimed polypeptide is involved with the above-mentioned activities, the asserted utilities are not substantial. Additionally, leucine rich repeat (LRR)-containing proteins are a diverse group of molecules with differing functions and cellular locations in a variety of organisms (Kobe et al. Trends in Biochem Sci 19(10): 415-421, 1994; pg 415, ¶ 1; pg 419-420). Although LRR-containing proteins are involved in protein-protein interactions and at least half of them take part in signal

transduction pathways, few properties are shared among all members of the LRR superfamily (pg 419 Kobe et al.). Therefore, each new LRR-containing protein needs to be evaluated empirically to determine the precise role(s) it plays. Since the utility is not presented in mature form and significant further research is required, the utility is not substantial. The specification asserts the following as patentable utilities for the claimed putative polypeptide (SEQ ID NO: 245):

1) to produce a variant polypeptide (pg 113-116)

2) to screen for peptides/ligands/small molecules which specifically bind the polypeptide (pg 124, lines 22-32; pg 128-130)

3) in tissue typing (pg 126, lines 24-26)

4) to produce antibodies against the polypeptide (pg 139-140)

5) PDB12 cell inhibition (pg 207, lines 2-18)

6) stimulation of adult heart hypertrophy (pg 207, lines 20-32)

Each of these shall be addressed in turn.

1) to produce a variant polypeptide. This asserted utility is credible but not substantial or specific. Such assays can be performed with any polypeptide. Further, the specification discloses nothing specific or substantial for the variant polypeptide that is produced by this method. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

2) to screen for peptides/ligands/small molecules which specifically bind the polypeptide. This asserted utility is credible and substantial but not specific. Such assays can be performed with any polypeptide. Additionally, the specification discloses nothing specific or substantial for

the agents that can be identified by this method. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

3) in tissue typing. This asserted utility is credible but not substantial or specific. Such assays can be performed with any polypeptide. Further, the specification does not disclose specific amino acid sequences for use as markers. The specification also does not disclose the tissue(s) that PRO293 is normally or abnormally present in. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

4) to produce antibodies against the polypeptide. This asserted utility is credible and substantial but not specific. Antibodies can be made to any polypeptide. However, if the specification discloses nothing specific and substantial about the polypeptide, therefore both polypeptide and its antibodies have no patentable utility.

5) PDB12 cell inhibition. This asserted utility is not credible, specific or substantial. The specification teaches that "a percent decrease in protein production of greater than or equal to 25% as compared to the negative control cells is considered positive" (pg 207, lines 16-17). However, any slight decrease in protein production, which may even result from the normal variations in cell number, would not indicate that PRO293 specifically inhibits protein production in PDB12 pancreatic ductal cells. Although the specification teaches that PRO293 is positive in this assay, the specification does not disclose any specific resulting cell numbers or percentages, statistical differences, or the number of repetitions for the assay. Without this knowledge, which could not be gleaned from the instant specification, one of ordinary skill in the

art at the time the invention was made would not have been able to use the information obtained from this assay in a useful manner. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial. Furthermore, the specification of the instant application teaches that PRO polypeptides that inhibit protein production in PDB12 pancreatic ductal cells are useful in the therapeutic treatment of disorders which involved protein secretion by the pancreas, including diabetes, and the like (pg 207, lines 3-5). This asserted utility is not credible, specific, or substantial. The specification does not disclose any disorders which involve protein secretion by the pancreas which are associated with altered levels or forms of the PRO293 polypeptide. Significant further experimentation would be required of the skilled artisan to identify individuals with such a disease. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

6) stimulation of adult heart hypertrophy. This asserted utility is not credible, specific, or substantial. The specification teaches that "any degree of growth enhancement as compared to the negative control cells is considered positive for the assay" (pg 207, lines 30-31). However, any slight increase in cell growth, which may even result from the normal variations of the cell media, would not indicate that PRO293 specifically enhances myocyte cell growth. Although the specification teaches that PRO293 is positive in this assay, the specification does not disclose any specific resulting cell numbers, stastical differences, or the number of repetitions for the growth assay. The specification also does not teach what type of "cell growth" is measured in the assay (i.e., cell proliferation, cell differentiation). Without this knowledge, which could not be gleaned from the instant specification, one of ordinary skill in the

art at the time the invention was made would not have been able to use the information obtained from this assay in a useful manner. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial. Furthermore, the specification of the instant application teaches that PRO polypeptides that stimulate the growth of adult ventricular myocytes are useful for the therapeutic treatment of various cardiac insufficiency disorders (pg 207, lines 21-23). This asserted utility is not credible, specific, or substantial. The specification does not disclose any cardiac insufficiency disorders which are associated with altered levels or forms of the PRO293 polypeptide. Significant further experimentation would be required of the skilled artisan to identify individuals with such a disease. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

7. Claims 39-51 also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

8. Furthermore, claims 39-43 and 50-51 are directed to an isolated polypeptide having at least 80%, 85%, 90%, 95%, and 99% amino acid sequence identity to (a) the amino acid sequence of the polypeptide shown in Figure 86 (SEQ ID NO: 245), (b) the amino acid sequence of the polypeptide shown in Figure 86 (SEQ ID NO: 245) lacking its associated signal peptide, (c) the amino acid sequence of the extracellular domain of the polypeptide shown in Figure 86 (SEQ ID NO: 245), (d) the amino acid sequence of the extracellular domain of the polypeptide

shown in Figure 86 (SEQ ID NO: 245) lacking its associated signal peptide, or (e) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209393.

The specification teaches that the term "'PRO/number polypeptide' and 'PRO/number' wherein the term 'number' is provided as an actual numerical designation as used herein encompass native sequence polypeptides and polypeptide variants. The PRO293 polypeptides described herein may be isolated from a variety of sources, such as from human tissue types or from another source, or prepared by recombinant or synthetic methods (pg 66, lines 2-8). The specification also discloses that a native sequence of PRO293 polypeptide may encompass "naturally-occurring truncated or secreted forms of the specific PRO polypeptide, naturally-occurring variant forms and naturally-occurring allelic variants of the polypeptide" (pg 66, lines 9-14). However, the specification does not teach any variant PRO293 polypeptide other than the full-length protein of SEQ ID NO: 245. The specification does not disclose methods or working examples to enable one skilled in the art to obtain a "naturally occurring allelic variant" or any allelic variants from different species. The specification also does not teach functional or structural characteristics of the polypeptide fragments recited in the claims.

The problem of predicting protein and DNA structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and DNA is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various

sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex

nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

9. Claims 39-43 and 50-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 39-43 and 50-51 are directed to an isolated polypeptide having at least 80%, 85%, 90%, 95%, and 99% amino acid sequence identity to (a) the amino acid sequence of the polypeptide shown in Figure 86 (SEQ ID NO: 245), (b) the amino acid sequence of the polypeptide shown in Figure 86 (SEQ ID NO: 245) lacking its associated signal peptide, (c) the amino acid sequence of the extracellular domain of the polypeptide shown in Figure 86 (SEQ ID NO: 245), (d) the amino acid sequence of the extracellular domain of the polypeptide shown in Figure 86 (SEQ ID NO: 245) lacking its associated signal peptide, or (e) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209393. The claims do not require that the polypeptide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polypeptides that is defined only by sequence identity.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus.

The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. Additionally, the description of one polynucleotide species (SEQ ID NO: 244) and one polypeptide species (SEQ ID NO: 245) is not adequate written description of an entire genus of functionally equivalent polynucleotides and polypeptides which incorporate all variants and fragments and with at least 80%, 85%, 90%, 95%, and 99% sequence identity to polypeptide comprising the amino acid sequence of SEQ ID NO: 245.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement

that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only an isolated polypeptide consisting of the amino acid sequence of SEQ ID NO: 245, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 39-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. The protein identified as PRO293 is a soluble protein, and is not disclosed as being expressed on a cell surface. Accordingly, the limitation that the claimed protein comprises an "extracellular domain" (for example see claim 39 parts (c) and (d)) is indefinite, as the art does not recognize soluble proteins as having such domains. Further, if the protein had an

extracellular domain, the recitation of "the extracellular domain"... "lacking its associated signal sequence" (claim 39, part (d), for example) is indefinite as a signal sequence is not generally considered to be part of an extracellular domain, as signal sequences are cleaved from said domains in the process of secretion from the cell.

Conclusion

No claims are allowable.

The art made of record and not relied upon is considered pertinent to applicant's disclosure:

Hayata et al. Gene 221 : 159-166, 1998.

Taguchi et al. Mol Brain Res 35(1-2) 31-40, 1996.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

Elizabeth C. Kennedy

BEB
Art Unit 1647
September 25, 2002

ELIZABETH [illegible]
PRIMARY EXAMINER